

CEPHALORIDINE IN GONORRHOEA AND SYPHILIS*†

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Cephaloridine is a new semi-synthetic antibiotic obtained from Cephalosporin C which is derived naturally from the mould *Cephalosporium acremonium*. It is a pyridine salt of the 7-aminocephalosporanic acid, produced in this country under the name of Ceporin by Glaxo Research Laboratories. Another semi-synthetic product of Cephalosporin C, sodium cephalothin or Keflin, has been in use for a few years in the U.S.A. The cephalosporins have a chemical structure similar to the penicillins, but have a different nucleus.

Clinical experience with cephaloridine is limited, but from the few published papers it would appear that cephaloridine does not readily cause hypersensitivity and that it is not cross-allergenic with penicillin (Murdoch, Speirs, Geddes, and Wallace, 1964). It has been successfully used in infections with organisms resistant to other antibiotics, in particular to penicillin, and most impressive results were attained in urinary infections (Stewart and Holt, 1964; Ishigami, Hara, and Shoji, 1965; Lenti, Pellegrini, Pagano, and Pisani, 1966).

Cephaloridine is poorly absorbed from the gastrointestinal tract and is therefore given by injection. Satisfactory blood levels can be maintained by a dose of 250 to 500 mg. 8 to 12-hourly (Barber, 1965). It is excreted in the urine almost entirely unchanged and a dose of 500 mg. to 1 g. produces high urinary concentrations for 24 hours (Muggleton, O'Callaghan, and Stevens, 1964; Murdoch and others, 1964). It is inactivated by penicillinase more slowly and considerably less than benzylpenicillin (Ridley and Phillips, 1965; Wick and Boniece, 1965). It is virtually non-toxic, though in recent experimental studies on animals Child and Dodds

(1966) noted that large doses of cephaloridine produced proximal renal tubular necrosis; this nephrotoxic action could be prevented by probenecid.

Like penicillin, cephaloridine is bactericidal. Its antibacterial spectrum includes *Neisseria gonorrhoeae*. Barber and Waterworth (1964) compared the antibacterial activity of five penicillinase-resistant penicillins and the two cephalosporins (cephalothin and ceph. 87/4, as cephaloridine was then known) with the activity of benzylpenicillin. Cephaloridine showed the lowest activity in 25 strains of gonococci tested (4 µg. as compared with 0.03 to 0.06 µg. methicillin in penicillin-sensitive strains). Strains with increased resistance to benzylpenicillin were also more resistant to the other antibiotics, including cephaloridine. Also the few strains of *Neisseria gonorrhoeae* tested by Muggleton and others (1964), Ødegaard (1965), and Wick and Boniece (1965) required much higher minimum inhibitory concentrations of cephaloridine than strains of other sensitive organisms. In contrast, the growth of the strain tested by Bernard and Bunaux (1965) was inhibited by 0.25 µg. cephaloridine.

The purpose of this paper is to give an account of the results of a clinical trial of cephaloridine in gonorrhoea and of an experience with its use in syphilis. In addition the results obtained in a small series of cases of non-gonococcal urethritis in the male are reported.

Gonorrhoea

Material and Methods

Two series of patients were treated at the V.D. Clinic of St. Luke's Hospital in Bradford.

(1) A series of seventy cases of uncomplicated urethral gonorrhoea in 67 male patients (three re-infected patients were treated twice) was treated during the first 3½ months of 1965. Fifty received a

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single dose of 1 g. and twenty two doses of 500 mg. at an interval of 6 to 8 hours by deep intramuscular injection.

(2) A series of 115 male and fourteen female patients was treated from September, 1965, to February, 1966, and a few later, with a single injection of 2 g.

Three more patients, one male who was hypersensitive to penicillin, and one male and one female who had not responded to penicillin, were treated with a single dose of 1 g. in June, 1965. The two male patients were included in the first series.

The ages of the male patients ranged from 15 to 64 years, the majority being in the 25 to 35-year age group; the ages of the females ranged from 16 to 33 years (average 26).

In both men and women treatment was given immediately after gonococci were found in the smears. In all cases, however, chocolate agar plates were inoculated and sensitivity tests with 0.125 unit penicillin and 5 µg. cephaloridine disks and fermentation tests were performed. In the majority of cases the gonococcus was tested also for disk-sensitivity to streptomycin (20 µg.). In cases in which the 0.125 unit penicillin disk failed to inhibit the growth of gonococci *in vitro* and which after failure of penicillin were re-treated with cephaloridine, the organisms were tested by the disk method against higher concentrations of penicillin and against other antibiotics. In three cases in the first series and in eight in the second, all males, the cultures were negative. A Wassermann reaction, VDRL test, and GCF test were performed routinely at the patients' first attendance.

Follow-up

Males After treatment those male patients who at any stage did not default from follow-up were examined twice during the first week, then weekly for 2 or 3 weeks, and once more after 3 months, when a final blood test was carried out. If at any stage a urethral discharge was present, smears and cultures were taken. After 3 or 4 weeks an examination per rectum was carried out and the fluid expressed by prostatic massage was examined by smear and culture. If no gonococci were found the patient was regarded as cured. In five cases in the first, and in ten in the second series, these tests for cure were performed earlier, usually after 14 days, when it was thought advisable to start treatment with other antibiotics for a concomitant non-gonococcal urethritis. In a number of patients who

at first ceased to attend, the tests were performed later when they re-attended in response to a recall letter or social worker's visit or returned of their own accord with another condition; in one case this happened after 14 months. A case was considered to be a treatment failure when gonococci were found in the urethral discharge within 14 days even if re-infection was suspected, but sexual re-exposure was denied by the patient, or when gonococci were detected in the fluid expressed by prostatic massage. Re-infection was determined by the patient's own admission of re-exposure or by the sensitivity pattern of the gonococcus *in vitro*. The time of re-infection varied widely from 11 days to 11 months.

Females The women were examined weekly at least three times and then twice after the menses, and a final blood test was performed after 3 months. The patient was considered cured when three consecutive urethral and cervical smears and cultures, including one post-menstrual examination, were negative. In fact, the majority completed the full 3 months' period of surveillance and an additional criterion of cure was provided in married couples by the absence of a relapse in either consort after resumption of marital relations.

Results

Males The results in the first series of patients are shown by dosage schedule in Table I, and by race in Table II (opposite).

The failure rate in the group of UK-born whites was more than three times greater than in the other three groups between which it was almost equally distributed. Failure became apparent within 3 to 5 days in eight cases and after 7 days in one case; in one case gonococci were found by smear and culture in the fluid expressed by prostatic massage 3 weeks after treatment and in one the smear and culture were positive after 24 hours; in this case the gonococcus was found to be resistant *in vitro* to cephaloridine, streptomycin, and 0.25 units penicillin. The three patients who were treated twice, all Negroes, were re-infected after 12, 28, and 30 days respectively, the two latter after satisfactory tests for cure; on the second occasion all three were classified as cured. Of the two patients who were excluded, one was admitted to hospital with Reiter's disease within a few days and was then treated with other antibiotics and the second had primary syphilis for which treatment with penicillin was started the next day.

TABLE I
RESULTS OF TREATMENT WITH 1 g. CEPHALORIDINE (MALES)

Dosage Schedule	Treated	Cured	Reinfected	Defaulted	Excluded	Failed	Failure Rate (per cent.)
Single Injection	52	29	6	8	2	7	13.8
Two 0.5 g. Injections	20	10	2	4	—	4	20.0
Total	72	39	8	12	2	11	15.3

TABLE II
RESULTS OF TREATMENT WITH 1 g. CEPHALORIDINE, BY RACIAL GROUPS (MALES)

Race	Treated	Cured	Reinfected	Defaulted	Excluded	Failed	Failure Rate (per cent.)
Asians	35	21	4	6	—	4	11.4
W. Indians and Other Negroes	17	9	3	3	—	2	11.7
UK-born Whites	11	4	1	1	1	4	36.3
Other Whites	9	5	—	2	1	1	11.1
Total	72	39	8	12	2	11	15.3

In the second series (Table III) 116 treatments were performed in 115 cases. One patient, who successively at weekly intervals failed to respond to 2 g. cephaloridine, 1.2 mega units procaine penicillin, and 3 g. spiramycin, was successfully re-treated with 2 g. cephaloridine. There were thus, in fact, only five cases which failed to respond, though there were six treatment failures. There

were no failures in the largest group of 55 Asians, and five of the six failures occurred in the group of UK-born whites. Three patients, two Asians and one West Indian, had been previously treated with success with 1 g. cephaloridine and were also included in the first series.

Treatment failures in this group are analysed in Table IV (overleaf). All six were tall and heavily built and weighed more than 75 kg. In contrast, the average weight of the Asians was approximately 55 kg. In five of these failures the gonococcus showed a reduced sensitivity to penicillin and was resistant to streptomycin *in vitro*, but only in one case was it resistant to 5 µg. cephaloridine. Failure became apparent in four cases within the first 3 days, in one after a week, and in one after 12 days; in the last case re-infection was suspected.

TABLE III
RESULTS OF TREATMENT WITH A SINGLE INJECTION OF 2 g. CEPHALORIDINE, BY RACE (MALES)

Race	No. of Treatments	Cured	Re-infected	De-faulted	Failed	Failure Rate (per cent.)
Asians	55	52	2	1	—	—
West Indians & Other Negroes	18	9	4	4	1	5.5
UK-born Whites	37	24	2	6	5	13.5
Other Whites	6	3	—	3	—	—
Total	116	88	8	14	6	5.2

Females Only one woman was treated with a single injection of 1 g. cephaloridine after penicillin failure; she failed to respond and was later successfully re-treated with penicillin and probenecid.

The group of fourteen women treated with 2 g. (Table V, overleaf) had no failures; twelve of them were English, one was Irish, and one was a West Indian girl aged 16 years who had given birth to her second child a fortnight previously and was

TABLE IV

TREATMENT FAILURES WITH 2 g. CEPHALORIDINE IN SIX MALES

Case No.	Race	Age (yrs)	Marital Status	Occupation	Sensitivity of the Gonococcus <i>in vitro</i>
1	UK-born	42	Married	Labourer	Reduced to penicillin Resistant to streptomycin
2	West Indian	43	Separated	Labourer	Reduced to penicillin Streptomycin not tested
3	UK-born	39	Single	Engineer	Reduced to penicillin Resistant to streptomycin
4	UK-born	54	Separated	Lorry driver	Reduced to cephaloridine and penicillin Resistant to streptomycin
5	UK-born	33	Married	Lorry driver	Reduced to penicillin Resistant to streptomycin
6	UK-born	21	Single	Soldier	Sensitive to cephaloridine, penicillin (0.125 units), and streptomycin

TABLE V

RESULTS IN 14 FEMALE PATIENTS TREATED WITH 2 g. CEPHALORIDINE

Male Consorts		No. Treated	Cured	Re-infected	De-faulted
Treated with 2 g. Cephaloridine	Cured	6	6	—	—
	Failed Re-infected	1	—	2	—
Treated otherwise		2	1	—	1
Not known		3	1	—	2
Total		14	9	2	3

referred to the clinic because the child had gonococcal ophthalmia. Seven of the women had a concomitant trichomonal infection which was treated with oral metronidazole, and one had candidiasis which was treated with Amphotericin B pessaries. The two re-infected couples were promiscuous West Indians with their equally promiscuous Bradfordian girl-friends. In one couple the gonococcus was found to be resistant to 0.125 unit penicillin *in vitro* on the first occasion, but was fully sensitive on the second. The other couple re-attended after 10 weeks, both admitting sexual exposure with somebody else. The sensitivity pattern *in vitro* was congruous in each of the eleven pairs of sexual partners tested.

Sensitivity Tests *in vitro* and Clinical Response

In forty cases the gonococcus showed *in vitro* a reduced sensitivity or resistance to one or more antibiotics (Table VI, opposite). In the seven cases in which 5 µg. cephaloridine disks failed to inhibit the growth of gonococci, the organisms were resistant also

to 0.125 or 0.25 unit penicillin and 20 µg. streptomycin disks. Nevertheless, of the six cases treated with 2 g. cephaloridine, only one failed. There was, however, a definite correlation between the clinical response and reduced sensitivity of the gonococcus to penicillin. This is shown at the bottom of Table VI and in the Figure. Eight of the patients with reduced sensitivity *in vitro* were treated with cephaloridine after failure of 1.2 mega units procaine penicillin. Two, a man and a woman, were

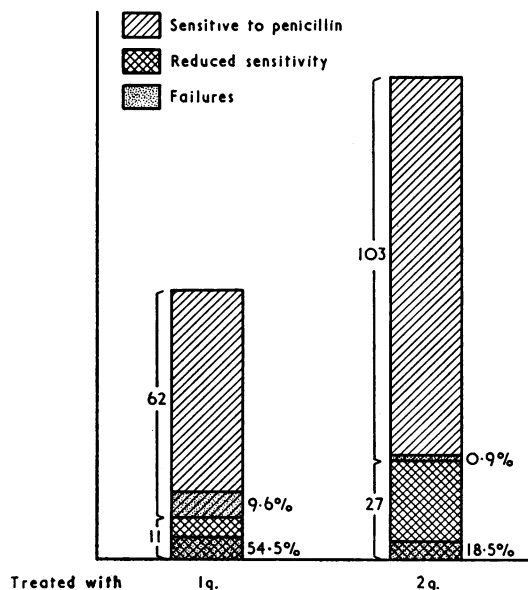


FIGURE.—Results of sensitivity tests.

TABLE VI

RESULTS IN CASES WITH REDUCED SENSITIVITY OF THE GONOCOCCUS TO ANTIBIOTICS IN VITRO

Reduced Sensitivity or Resistance to:		Dosage (g.)					Totals	
		1 or 0.5 × 2			2			
		Cure	Failure	Default or Re-infection	Cure	Failure		Default or Re-infection
Cephaloridine (5 µg.) Penicillin (< ½ unit) Streptomycin (20 µg.)		—	1	—	4	1	1	7
Penicillin Streptomycin		1	2*	1	7	3	2	16
Penicillin (in 12 cases streptomycin not tested)		3	3	—	6	1	2	15
Streptomycin		—	—	1	1	—	—	2
Total		4	6	2	18	5	5	40
Failure Rate (per cent.)	in cases with reduced sensitivity to penicillin	54.5 (6 in 11)			18.5 (5 in 27)			
	in cases sensitive to 0.125 units penicillin	9.6 (6 in 62)			0.9 (1 in 103)			

* In one case reduced sensitivity also to tetracycline.

treated with 1 g. and both failed, but the six, four men and two women, who received 2 g. were all cured.

Syphilis

Antitreponemal Action of Cephaloridine *in vivo*

The effect of cephaloridine on *T. pallidum* was tested in two cases of primary syphilis before treatment with penicillin was started.

(1) *An Irishman aged 30 years* had an erosion on the glans penis. On dark-field examination, numerous treponemes were found in the serum from the lesion before he received an injection of 1 g. cephaloridine, and no treponemes could be found in several specimens examined 24 hours later. He reported that during the night after the injection he had felt feverish and had a headache. This patient was one of the two who were excluded from the first gonorrhoea series.

(2) *An Englishman aged 21 years* had a dark-field positive erosion on the penis with one to four treponemes in each microscopic field viewed. After an injection of 1 g. cephaloridine he was admitted to hospital and the rate of disappearance of treponemes from the lesion was studied by 2-hourly dark-field examinations. After 2 hours numerous treponemes were still seen, but about 50 per cent. of the organisms were not motile; after 4 hours there were considerably fewer treponemes (one in four microscopic fields) and the majority were non-motile. After 6 hours one dead treponema was detected in six specimens examined. No treponemes were found in several specimens examined after 8 hours and again

after 24 hours. In this case there was no evidence of a Herxheimer reaction.

A Case of Secondary Syphilis treated with Cephaloridine

(3) *An unmarried white girl aged 20 years* presented in May, 1965, with indurated oedema of the right labium majus and painless swelling of lymph nodes in the right groin. No treponemes were detected in puncture fluid from the oedematous labium and from an inguinal node, but two days later a papular rash appeared on the trunk and limbs, and the blood Wassermann reaction was positive at 1 in 40 dilution; the VDRL slide test and RPCF test were also positive. A year previously she had had a severe cutaneous reaction after an injection of penicillin. She was 4 months pregnant and was suffering from neurotic hyperemesis, which rendered difficult treatment by mouth. It was decided to treat her with cephaloridine. She was admitted to hospital and was given an initial dose of 1 g. and 500 mg. 8-hourly for 4 days and 1 g. 12-hourly for 10 days. She had a Jarish-Herxheimer reaction with temperature raised up to 102°F. and a further dissemination of papules was noted on the following morning. Then the papules started to fade rapidly and disappeared completely within 5 days; the labial oedema resolved more slowly and was still slightly in evidence when she was discharged from hospital on the 15th day (June 1). The standard Wassermann reaction was negative with serum from a specimen of her blood collected on that day, but the serum was reactive with the cardiolipin, VDRL, and Reiter protein antigens. A month later the cardiolipin Wassermann became doubtful. At that time her regular consort was found to be suffering from

sero-positive primary syphilis and she was persuaded to re-enter hospital for a further course of cephaloridine as a preventive measure. Treatment was started 7 weeks after her previous discharge from hospital, and she was given 500 mg. twice daily for 10 days. On the day treatment was started the Wassermann reaction was positive at 1 in 20. As she had been repeatedly at risk this was regarded as indicating a re-infection rather than a serological relapse. At the end of the 10 days' course of treatment, the Wassermann reaction reverted to a doubtful reading. She was once more treated with cephaloridine in August, *i.e.* a month later, when she was found to be suffering from gonorrhoea complicated by salpingitis. She received 500 mg. three times daily for a week with very good response. By then the standard Wassermann was negative, the cardiolipin Wassermann doubtful, and the VDRL and RPCF tests positive. She was delivered of a healthy child in November, when the Wassermann reaction was negative with both the standard and cardiolipin antigens, but the VDRL and RPCF tests were still positive. In April, 1966, the RPCF and treponemal immobilization tests were weakly reactive and the reagin tests were negative. The child's blood was tested in February, 1966, when he was 3 months old, and the Wassermann reaction, VDRL, and RPCF tests were all negative.

Non-gonococcal Urethritis

Sixteen male patients, eleven Pakistani, four English, and one West Indian, were given an injection of 1 g. cephaloridine daily for 3 days. The urethral discharge ceased and did not recur in five cases, but there was no clinical improvement in eleven (62.5 per cent. failure rate). In two of the latter patients *T. vaginalis* was later detected.

Side-Effects

Cephaloridine was tolerated very well and the injections were virtually painless. There were no side-effects whatever in the penicillin-sensitized patient who received three courses of 33, 20, and 21 injections respectively, or in the group of sixteen patients who were treated with three daily injections for non-gonococcal urethritis, or in the seven who had two treatments for gonorrhoea.

Two patients treated with a single injection of 2 g. had an allergic reaction of the angioneurotic oedema/urticaria type 2 days after treatment. One, a Pakistani aged 30 years, had no history of previous injections; the other, a West Indian aged 25, had had several previous gonorrhoeal infections treated with penicillin and had had a similar, but more severe, reaction after an injection of procaine penicillin 3 weeks previously.

Discussion

The results of this clinical trial suggest that cephaloridine has a very potent antigonococcal action *in vivo*, in spite of the laboratory evidence that it is much less active against *Neisseria gonorrhoeae* than benzylpenicillin. There was only one failure in 103 penicillin-sensitive cases treated with a single injection of 2 g. In such cases, however, cephaloridine is not indicated, and its indiscriminate use may well result in the emergence of cephaloridine-resistant strains of gonococci.

There are three possible indications for the use of cephaloridine in gonorrhoea: penicillin failure, penicillin-sensitization, and rectal infection.

In cases in which penicillin has failed, the frequent association of reduced sensitivity of the gonococcus to penicillin with resistance to streptomycin (almost 90 per cent. in our experience) has rendered streptomycin virtually useless. Although there is a similar correlation between penicillin and cephaloridine, a dose of 2 g. of the latter has succeeded in the overwhelming majority of cases with reduced sensitivity to penicillin. Analysis of the failures suggests that this dose may not be sufficient if related to the weight of some patients. If the dosage was calculated according to body weight, *i.e.* 30 mg./kg., the risk of failure could be minimized.

In penicillin-sensitized cases, one has to take into account the possibility of a cross-reaction between penicillin and cephaloridine. It is now generally accepted after Levine (1960) and Levine and Ovary (1961) that the antigenic determinant in benzylpenicillin hypersensitivity is formed by the conjugation to tissue protein of the highly-reactive benzylpenicillenic acid, a degradation product of the penicillin nucleus. Benzylpenicillenic acid does not occur in the process of degradation of the cephalosporins and there should be no cross-reactivity between the two groups of antibiotics. However, Brandriss, Smith, and Steinman (1964) have demonstrated in rabbits that a cross-reaction may occur through a different chemical re-arrangement involving the β -lactam ring which is fused with the penicillin as well as the cephalosporin nucleus. It is possible that this unusual mechanism was responsible for the allergic reaction to cephaloridine in our penicillin-sensitized patient, and in the patient reported by Kabins, Eisenstein, and Cohen (1965), who had an immediate anaphylactoid reaction to an initial dose of 500 mg. sodium cephalothin

3 weeks after an injection of 600,000 units penicillin G. On the other hand, many patients known to be sensitized to penicillin were treated with either cephalothin (seven in the series of Griffith and Black, 1964) or cephaloridine (two in the series of Seftel, 1965) with no adverse reactions ensuing; also Stewart and Holt (1964) administered cephaloridine intradermally to five subjects with proven cutaneous hypersensitivity to penicillin and there were no local or systemic reactions.

In our series, besides the girl who received three courses of treatment, there were two more penicillin-sensitized patients who were given cephaloridine with no ill-effects. It seems, therefore, that the type of penicillin-hypersensitivity which cross-reacts with the cephalosporins is rare.

In rectal gonorrhoea the use of cephaloridine may be considered because of the possible presence of penicillinase-forming bacteria, which may invalidate the action of benzylpenicillin. We had no opportunity to test this indication.

Cephaloridine appears to have also a powerful antitreponemal action, and the immediate clinical and serological response in Case 3 was comparable with that attained with penicillin. Although it is now a year since she was first treated, in view of her probable re-infection and the two further courses of treatment she has had, it is not possible to evaluate the case in terms of cure, especially as the cerebrospinal fluid has not yet been tested. Cephaloridine apparently does not pass the blood-brain barrier in appreciable quantities (Murdoch, 1965), which makes routine examination of the cerebrospinal fluid all the more important.

Similarly, good immediate clinical results in early syphilis are reported by Seftel (1965) and Seftel, Sieff, and Richardson (1966) from the Non-European Hospital in Johannesburg and by Ochoa and Cravioto (1965) from Mexico. Galla, Pagnes, and Ferrari (1965) report from Italy that they have cured experimental testicular syphilis in rabbits with three daily intramuscular injections of cephaloridine 5 mg./kg. body weight.

In syphilis, sensitization to penicillin is the only indication for the use of antibiotics other than penicillin. If further clinical trials with an adequate follow-up period proved cephaloridine to be curative, it would provide an excellent alternative to penicillin, particularly in pregnancy, in which tetracycline is contra-indicated and hyperemesis may not permit treatment with erythromycin or other antibiotics administered by mouth. The dosage of cephaloridine in early syphilis has yet to be established; it may well be that a daily injection of 2 g.

for 10 or 14 days (with or without probenecid) may be adequate and this would enable treatment to be given on an out-patient basis.

In non-gonococcal urethritis, the results were not impressive, as one would expect with an antibiotic so similar to penicillin in its action.

Finally, Vegas (1965) reports from Venezuela that he has successfully treated three cases of lymphogranuloma venereum with 1 g. cephaloridine daily for 6, 8, and 9 days respectively.

Summary

(1) 202 cases of gonorrhoea, 187 males and 15 females, were treated with cephaloridine (Ceporin). Of the males, 72 were given 1 g. either by two injections of 0.5 g. (20 patients) or by a single injection (52 patients), and 115 received a single injection of 2 g. The failure rate was 15.3 per cent. (20.0 and 13.8) and 5.2 per cent. respectively, but one of the six patients who failed with 2 g. was later successfully re-treated with the same dose of cephaloridine after penicillin and spiramycin had failed. Of the females, one was unsuccessfully treated with 1 g. after failure with penicillin, but there were no failures in the group of fourteen who were treated with 2 g.

There was a definite correlation between failure of cephaloridine and reduced sensitivity of the gonococcus to penicillin *in vitro*. In the group of patients treated with 1 g., there were six failures in eleven cases with reduced sensitivity to penicillin (54.5 per cent.) as opposed to six failures in the remaining 62 cases (9.6 per cent.); in the group treated with 2 g., there were five failures in 27 cases with reduced sensitivity to penicillin (18.5 per cent.) against only one in the remaining 103 (0.9 per cent.).

Treatment failures were related also to the weight of the patients, and the six who failed with 2 g. cephaloridine all weighed more than 75 kg., where as there was not a single failure among the 55 Asians whose average weight was approximately 55 kg.

(2) In two cases of primary syphilis, *T. pallidum* disappeared promptly from the primary lesion in response to an injection of cephaloridine given 24 hours before treatment with penicillin. A pregnant woman known to be sensitized to penicillin and suffering from hyperemesis gravidarum received a 14-day course of cephaloridine for secondary syphilis with a remarkable clinical and serological response. She was later given two more courses of cephaloridine, for a probable re-infection and for

gonococcal salpingitis, and there were no untoward reactions.

(3) Of sixteen males treated for non-gonococcal urethritis with three daily injections of 1 g. cephaloridine, eleven (62.5 per cent.) showed no clinical improvement.

(4) Cephaloridine was tolerated very well and the injections were virtually painless. Two patients treated with a single injection of 2 g. had an allergic reaction of the angioneurotic oedema/urticaria type; one of them had had a similar reaction after an injection of procaine penicillin 3 weeks previously. Three more patients known to be sensitized to penicillin, including the woman with secondary syphilis, received cephaloridine with no ill-effects.

(5) It is concluded that, in spite of the high efficacy of cephaloridine in gonorrhoea, its use should be limited to cases in which penicillin has failed (when the dosage should be calculated on the basis of 30 mg./kg. body weight) and to cases of penicillin-sensitization and rectal infection.

In syphilis, cephaloridine may provide an excellent alternative to penicillin in penicillin-sensitized patients, especially in pregnancy, but its efficacy in terms of cure and the optimum dosage have yet to be established.

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La céphaloridine dans le traitement de la blennorragie et la syphilis

RÉSUMÉ

(1) 202 cas de blennorragie comprenant 187 hommes et 15 femmes avaient été soignés avec la céphaloridine (Ceporan). 72 des hommes avaient reçu 1 gramme: 20 malades recevant deux injections de 0,5 gramme chacun et 52 recevant une injection d'un gramme tandis que les 115 autres avaient reçu une seule injection de 2 grammes. Le taux d'insuccès a été de 15,3 pour cent (20,0 et 13,8) et 5,2 pour cent respectivement, mais un des six malades qui n'avait pas été guéri avec deux grammes avait été plus tard resoigné avec succès par la même dose de céphaloridine après un échec avec la pénicilline et la spiramycine. Des femmes, une avait été traitée sans succès avec un gramme après un échec avec la pénicilline mais il n'y avait pas eu d'échecs chez les 14 autres du groupe qui avaient été traitées avec deux grammes.

Il y avait une corrélation nette entre l'insuccès du traitement avec la céphaloridine et la sensibilisation réduite au gonocoque à la pénicilline *in vitro*. Dans le groupe des malades qui avaient reçu un gramme il y avait eu six cas d'insuccès parmi les onze cas montrant une sensibilisation réduite à la pénicilline (54,5 pour cent) contre six cas d'insuccès parmi les 62 autres cas (9,6 pour cent) du groupe qui avaient été traités avec 2 grammes, il y avait 5 cas d'insuccès chez les 27 malades montrant une sensibilisation réduite à la pénicilline (18,5 pour cent) contre un seul cas parmi les autres 103 cas (0,9 pour cent).

Les échecs qui avaient suivi le traitement avaient été aussi en rapport au poids des malades, et les six cas qui n'avaient pas été guéris par 2 grammes de céphaloridine pesaient plus de 75 kilos, tandis qu'il n'y avait pas eu un seul échec parmi les 55 asiatiques dont le poids était en moyenne de 55 kilos à peu près.

(2) Dans deux cas de syphilis primaire le *T. pallidum* avait disparu très vite de la lésion primaire à la suite d'une injection de céphaloridine donnée 24 heures avant le traitement par la pénicilline. Une femme enceinte connue comme étant allergique à la pénicilline et souffrant de vomissements incoercibles de la grossesse

avait reçu un traitement de 14 jours de céphaloridine pour une syphilis secondaire avec un résultat clinique et sérique remarquable. Plus tard elle avait reçu deux autres traitements avec la cephaloridine pour une re-infection probable et une salpingite blennorragique et il n'y avait pas eu de réactions fâcheuses.

(3) Des 16 hommes traités pour une urétrite non-blennorragique avec trois injections d'un gramme de céphaloridine par jour onze n'avaient pas montré une amélioration clinique.

(4) La céphaloridine avait été très bien tolérée et les injections avaient été presque sans douleur. Deux malades traités par une seule injection de deux grammes avaient montré une réaction allergique du type urticaire/œdème angio-neurotique un d'eux avait eu une réaction

identique après une injection de procaine pénicilline reçue trois semaines auparavant. Trois autres malades connus comme étant allergiques à la pénicilline y compris la malade atteinte de syphilis secondaire avaient reçu la céphaloridine sans effets fâcheux.

(5) Il a été conclu que malgré la grande efficacité de la céphaloridine dans la blennorragie, son usage doit être limité aux cas où la pénicilline a échoué (quand la posologie devrait être calculée sur la base de 30mg./kg. de poids) et aux cas montrant une allergie à la pénicilline et aux infections rectales.

Dans la syphilis la céphaloridine peut fournir une excellente alternative à la pénicilline chez les malades montrant une sensibilisation à la pénicilline, surtout pendant la grossesse, mais son efficacité comme cure et sa dosologie optimum restent encore à être établies.